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October 25, 1999

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Sub: Comments to Draft Guidance for Industry –
ANDAs: Blend Uniformity Analysis

Dear Sirs:

It was a great relief to see a draft guidance being issued with respect to Blend Uniformity Analysis for final mix blend prior to compression or encapsulation or other relevant unit operation(s) as described under Section II, SCOPE (on Page 2 of the draft guidance). I would like to congratulate the members of CMCCC group for undertaking the difficult task and provide an important guidance document in a timely manner.

I would like to provide my comments to this document as follows:

1. INTRODUCTION section:

1.1 The first paragraph states that, "... recommendations apply to ***original ANDAs and supplemental ANDAs for formulation and process changes.***"

The draft guidance is not very clear in the following aspects:

a. The guidance is retroactive or prospective. This is specifically for the requirements portion of ... "supplemental ANDAs for formulation and process changes."

b. If the firm has historical data showing no failure on content uniformity and no such requirements in their existing manufacturing controls, how a process formulation change in terms of the following will impact the uniformity aspect:

i) Deletion of some or entire portion of coating component(s)
ii) Deletion of color component from the composition

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iii) Minor process changes in coating process
iv) Minor changes in wet granulation drying conditions
v) Change in the wet granulation drying process
vi) Change in tablet compression or encapsulation equipment (use of an equipment with added controls)
vii) Minor composition changes allowed under SUPAC-IR Level I

c. For example: The firm had BUA controls in the manufacturing process for an approved application. This control was subsequently deleted through a prior approval supplement as described under 21 CFR 314.70(a)(2)(v). If this approved application goes through a minor composition change as described in SUPAC-IR Level I, what is the scientific rational of implementing BUA control?

1.2 The second paragraph states that, "... ***The in-process testing requirement for adequacy of mixing to ensure uniformity and homogeneity is established at 21 CFR 211.110(a)(3).***"

The reference made in this paragraph viz. 21 CFR 211.110 only refers to testing of in-process stage form of the final drug product. This drug product can either be a tablet, capsule or even a liquid or powder dosage form.

211.110 (a)(1), 211.110(a)(2) and 211.110(a)(4) refers to in-process samples of a tablet or capsule dosage form.

211.110(a)(3) and 211.110(g)(5) refers to in-process samples of a liquid dosage form where uniform mixing of solution, clarity, completeness, or pH of solutions are characteristic attributes for the liquid dosage form.

The section 21 CFR 211.110 no where requires testing of in-process components such as pre-mix, milled blend, final mix blend or individual components (excipients etc.) if going into making the final dosage form through various different unit operation(s).

The language provided under 21 CFR 211.110(b) requires a ***re-evaluation*** of applicability of this regulation in context to BUA testing requirements.

It should be noted here that adequacy of mixing of active pharmaceutical ingredients (APIs) with other components of drug product prior to formation of drug product is assured by process validation requirements and hence not necessary to be performed on every batch of drug product.

2. SCOPE Section:

2.1 The first paragraph states that "... BUA is recommended for those drug products for which the U.S. Pharmacopoeia (USP) requires content uniformity analysis." Does this mean that for a non-USP compendial product, there is no requirement for BUA testing?

The statement, "BUA is recommended for bioequivalence, test and commercial production batches of a drug product." This is a very general statement. It should be modified to state that, "BUA is recommended for process characterization of bio-equivalence batch and during process validation of commercial production batches of a drug product."

Reference is made here to the third paragraph of this section. There is indication of "complex dosage forms." I disagree with the use of word "complex". A modified release tablet or capsule dosage form is not necessarily a complex dosage form in terms of unit-operations employed in manufacturing these drug products.

I also disagree with the requirements for firms to consult appropriate reviewing division to determine if BUA is recommended. This is a resource issue. One wants reviewing division to allocate more time on issues related to reviewing of pending applications. This will create additional reviewing burden on all the divisions. Besides, in absence of any firm policy on these matters, each reviewer will tend to make an ad hoc decision based on the type of the product referred at a specific division.

The last paragraph of this section is again a misinterpretation of the regulation 21 CFR 211.110(a)(3). The extensive explanation is already provided in Item #1 of this letter. The firm also disagrees with the policy of not allowing any such deletion as described and allowed in 21 CFR 314.70(a)(2)(v).

3. SAMPLING SIZE AND PROCEDURES Section:

3.1 The firm agrees with agency's position on the recommended sample size of the blend material to be no more than three times the weight of an individual dose.

3.2 The firm also agrees with agency's position that in an event a sampling bias is encountered, the sample size should be increased to no more than ten times the weight of an individual dose.

3.3 The firm also agrees with agency's position on sampling from blender or drums of the blend. It is our understanding that sampling from drums is more meaningful as it evaluates any impact on blend characteristics during discharge of the blend into the drums. Moreover, blend contained in the drum is the final step prior to charging into hopper for the subsequent unit-operations viz. Compression, Encapsulation, etc.

3.4 Reference is made here to the third paragraph of this section. The firm disagrees with agency's position that BUA should be performed on all active ingredients present in the drug product. BUA testing should only be performed on the active component, which is present in the least quantity in the drug product. This is a worst case scenario and represents a scientifically meaningful evaluation of BUA.

3.5 The firm disagrees with the statement that "...weight of the sample tested should be equivalent to the dosage used." This should not be allowed. Once the unit dose sample (3 x dosage weight or 10 x dosage weight) is withdrawn, the entire sample shall be tested. Any subdivision of the BUA sample will not be a true representative of the actual sample. The subdivision of these samples will introduce more bias to the BUA sample.

3.6 The firm agrees with agency's position as stipulated in the fourth paragraph.

3.7 The firm recommends following alternative to the sampling bias encountered in the first set of samples:

> Second set of BUA samples with a "***different design***" of sample thief be allowed when the initial BUA results are not found acceptable.

3.8 The firm proposes an alternative to monitor adequacy of mixing to assure uniformity and homogeneity by implementing "Particle Size Analysis" test as an in-process control.

4. ACCEPTABLE CRITERIA ... Section:

4.1 The firm disagrees with the following:

BUA is CGMP requirements in terms of process validation. BUA should not be performed on each commercial production batch of a drug product.

4.2 For a drug product, containing 50 mg or less of active (or 50% or less of active), BUA should be performed on initial commercial batches of a drug product. Based on the significant body of data gathered, the firm should be

allowed to delete this in-process control through 21 CFR 314.70(a)(2)(v) regulation.

4.3 The proposed acceptance criteria should be revised to 90% to 110% (on mean value) with %RSD of not more than 5%. Rounding off should be allowed for this type of bulk testing.

4.4 BUA testing is more related to process validation activities and has no relevance to the terminology used, "...ensure compliance with USP."

As BUA testing itself is very complex, we recommend that it should be discussed in a public workshop with all the trade associations, academia and FDA personnel. Also the BUA requirements should be evaluated along the world harmonization efforts.

We acknowledge that it is an important issue and should be resolved in a scientific manner.

Please note that the very same topic was recently discussed at NAPM/GPIA/NPA/FDA fall workshop (Bethesda, Oct. 18-19, 1999). It is my understanding that FDA has concurred with the industry that this requires further discussion and a public/scientific forum to further evaluate validity of BUA concept in general.

The proposed guidance should not be made effective until such meetings and discussion with the agency and issuance of final BUA guidance.

Sincerely,

M. P Patel

Mahendra Patel, Ph.D.
Vice President

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